

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

From the nucleus to the mitochondria and backThe odyssey of a multitask STAT3

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/90191> since

Published version:

DOI:10.4161/cc.10.19.17379

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Marco Demaria, Valeria Poli

From the nucleus to the mitochondria and backThe odyssey of a multitask
STAT3

CELL CYCLE (2011) 10

DOI: 10.4161/cc.10.19.17379

The definitive version is available at:

<http://www.tandfonline.com/doi/abs/10.4161/cc.10.19.17379>

From the nucleus to the mitochondria and back

The odyssey of a multitask STAT3

Marco Demaria^{1,*} and Valeria Poli^{*}

Molecular Biotechnology Center; University of Turin; Turin, Italy

¹ Present address: Buck Institute for Research on Aging; Novato, USA

* Correspondence to: Valeria Poli; Email: valeria.poli@unito.it. Marco Demaria; Email: mdemaria@buckinstitute.org

STAT3, a member of the Signal Transducers and Activators of Transcription (STAT) family, is constitutively activated by phosphorylation on tyrosine 705 in a high percentage of tumors and tumor-derived cell lines of both liquid and solid origin, downstream of cytokines, growth factors and oncogenes¹. Tumor cells often become addicted to STAT3, as shown by the observation that interference with its transcriptional activity often triggers growth arrest and/or cell death. Importantly, STAT3 can also be phosphorylated on Serine 727 downstream of a number of stimuli leading to the activation of MAP kinases including RAS signaling². Although STAT3-mediated gene expression signature is mostly consistent with tumor cell survival and proliferation³, it varies in different tumor types, and a core activity determining addiction to STAT3 by a wide spectrum of biologically distinct tumors has not yet been identified.

To address this point, we have generated knock-in mice expressing physiological levels of the constitutively active STAT3C mutant form. Stat3C cooperates with the rat Neu oncogene triggering the production of more invasive mammary tumors via up-regulation of the focal adhesion protein CTEN⁴. In order to dissect the molecular functions of constitutively activated STAT3, we have analyzed primary mouse embryonic fibroblasts (MEF) derived from STAT3^{C/C} or STAT3^{WT/WT} mice⁵. STAT3^{C/C} MEFs showed increased proliferation, protection from apoptotic stimuli, decreased production of Reactive Oxygen Species (ROS) and delayed physiological senescence. Intriguingly, gene expression profiling revealed that STAT3^{C/C} cells down-regulated nuclear-transcribed mitochondrial genes, including many encoding for proteins belonging to the Electron Transport Chain (ETC) complexes, and up-regulated mRNAs involved in glycolysis, first of all Hypoxia Inducible Factor (HIF)-1 α .

Recently, STAT3 was shown to play an unconventional role in mitochondria⁶⁻⁸.

Mitochondrial STAT3 (mSTAT3) appears to sustain ETC basal activity under normal or RAS-transformed conditions, supporting RAS-dependent oncogenic transformation^{6,7}, and it was suggested to act as a negative regulator of the Mitochondrial Permeability Transition Pore (MPTP), thus mediating cardioprotection after ischemia/reperfusion⁸. Ser727 is required for mSTAT3 functions, but not Tyr705, nuclear localization or DNA binding activity. Indeed, activated RAS triggers Ser-phosphorylation rather than the conventional phosphorylation on Tyr, which in contrast confers nuclear localization and transcriptional activity and drives nuclear (n) STAT3 functions³. STAT3C mitochondrial localization was normal and mSTAT3 activities appeared to be preserved in the STAT3^{C/C} cells⁵. Nevertheless, mitochondrial activity and ATP production were reduced and could not be rescued by HIF-1 α silencing. Moreover, preliminary data suggest that the defective expression of several ETC proteins can be rescued upon STAT3 silencing (VP and M. Wieckowski, unpublished data), supporting the idea that the action of constitutively activated STAT3 on mitochondria is dominant and occurs primarily in the nucleus via direct or indirect transcriptional down-regulation of mitochondrial genes. Always in the nucleus, the constitutively activated STAT3 up-regulates transcription of the HIF-1 α gene, leading to HIF-1 α -mediated up-regulation of glycolysis including high glucose consumption and strong dependence on glucose for survival.

Thus, activated STAT3 acts as a master regulator of the metabolic switch from mitochondrial respiration to glycolysis occurring in most cancer cells and known as the ‘Warburg Effect’⁹, by promoting HIF-1 α -dependent aerobic glycolysis while depressing mitochondrial activity in a HIF-1 α -independent fashion. This switch is an important component of STAT3 pro-oncogenic activities, since inhibition of STAT3 tyrosine phosphorylation and dimerization via the small molecule inhibitor S3I in several STAT3-dependent tumor cell lines down-regulates glycolysis and enhances mitochondrial activity prior to leading to growth arrest and cell death, both *in vitro* and *in vivo*⁵. Moreover, primary STAT3^{C/C} MEFs become transformed and tumorigenic when immortalized via the 3T3 protocol, suggesting that constitutively active STAT3 can provide a first hit in the multi-step transformation process (MD et al., manuscript in preparation).

As depicted in Figure 1, at least two functionally distinct STAT3s exist: nSTAT3, acting in a conventional way to regulate gene transcription as a Tyr-phosphorylated dimer, and mSTAT3, which acts unconventionally to regulate mitochondrial functions, presumably requiring phosphorylation on Ser727. mSTAT3 preserves ETC activity both under basal and RAS-transformed conditions, and may provide protection from apoptosis upon stresses such

as ischemia/reperfusion by regulating MPTP opening⁶⁻⁸. Our data suggest that nSTAT3, when constitutively transcriptionally activated as it occurs downstream of oncogenic and inflammatory signals that trigger its tyrosine phosphorylation, promotes aerobic glycolysis and lowers cellular respiration, resulting in enhanced proliferation, resistance to hypoxia, glucose dependence and, importantly, decreased ROS production and resistance to apoptosis and senescence. Thus, although regulated downstream of different signals under distinct physiological or pathological conditions, nSTAT3 and mSTAT3 finally converge to enhance cell survival and protection from apoptosis via specific regulation of mitochondrial functions. Among other outstanding issues, it will be important to assess if and how the altered relative levels of Tyr-phosphorylated or Ser-phosphorylated STAT3 brought about by different oncogenic signals and inflammatory/stress conditions, altering the balance between nuclear and mitochondrial STAT3, can lead to an altered metabolic output.

ACKNOWLEDGMENTS

This study was supported by the Italian Cancer Research Association (AIRC). The authors wish to thank P. Pinton, C. Giorgi and M. Wieckowski for a fruitful collaboration.

FIGURE LEGEND

Figure 1. Converging roles of nuclear (n) and mitochondrial (m) STAT3. Different signals can selectively trigger STAT3 phosphorylation. Tyr-phosphorylated nSTAT3 (P-Y) mediates, among others, the up-regulation of HIF-1 α transcription and the down-regulation of mitochondrial genes, thus triggering faster proliferation¹⁰, decreased ROS production and resistance to apoptosis. On the other end, Ser-phosphorylated mSTAT3 (P-S) preserves ETC activity and regulates MPTP opening, ultimately also leading to apoptosis protection.

REFERENCES

1. Pensa S, et al. JAK-STAT Pathway in Disease 2009; 100-21.
2. Ceresa BP, et al. Endocrinology 1997; 138:4131-4137.
3. Yu H, et al. Nat Rev Cancer 2009; 9:798-809.
4. Barbieri I, et al. Cancer Res 2010; 70:2558-2567.
5. Demaria M, et al. Aging (Albany NY) 2010; 2:823-842.
6. Wegrzyn J, et al. Science 2009; 323:793-797.
7. Gough DJ, et al. Science 2009; 324:1713-1716.
8. Boengler K, et al. Basic Res Cardiol 2010; 105:771-785.
9. Warburg O. Science 1956; 123:309-314.
10. Vander Heiden MG, et al. Science 2009; 324:1029-1033.

Oncogenic/inflammatory signals

RAS, MAPK/stress signals

